Visual Analytic Approaches for the Analysis of Spontaneously-Reported Adverse Events in Post-Market Surveillance

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Safety Analyses

- Randomized clinical trials are the gold standard for evaluating the efficacy of a new intervention
- Development program provides an incomplete safety profile
  - Numerous safety endpoints (AE, labs, vitals, hospitalizations, QOL, ECG; multiplicity)
  - Rare safety events require greater sample size (power)
  - Studied in limited population
    - » Those most likely to respond for efficacy
    - » Those on few or no medications with limited other confounding diseases
  - Animals models may not be predictive (DILI)
  - Limited understanding of biological mechanisms and pathways

Safety Recalls

- Vioxx (rofecoxib). COX-2 inhibitors have increased CV risk and life-threatening GI bleeding
- Avandia (rosiglitazone). Increased CV risk.
- Rezulin (troglitazone). Liver failure
- Tysabri (natalizumab). Increased risk of PML (progressive multifocal leukoencephalopathy)

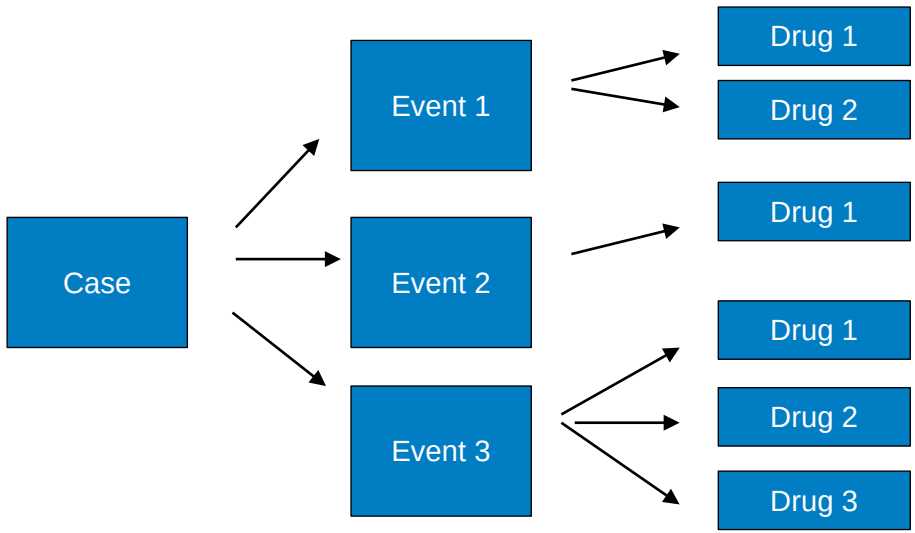
- Risk a therapy may pose may not be well understood until it has been on the market for many years, taken by individuals who differ from those studied under the inclusion criteria of the clinical development program

Spontaneously-reported adverse events

- Collected by regulatory agencies, pharmaceutical companies and device manufacturers to monitor the safety of a product once it reaches the market
- FDA maintains
  - AERS: Adverse Event Reporting System
  - VAERS: Vaccines Adverse Event Reporting System
  - MAUDE: Manufacturer and User Facility Device Experience
- Data are obtained from physicians, patients or medical literature

Data Structure

Figure 1. Data Structure



One record (row) per case-event-drug in a SAS formatted data set.
This example would have 6 rows.

Spontaneously-reported adverse events

- Unique challenges
  - No measure of total exposure (total number of subjects taking the drug)
  - No “control”
  - Data often inconsistently captured and of poor quality
- Of reported events, is a drug-event combination occurring more often than expected assuming independence between drug and events?
- Important:
  - No guarantee drug caused event
  - Number of cases not equal to number of people. Can get multiple reports from same person
  - Cannot calculate incidence

Pharmacovigilance: Disproportionality Analysis

Table 1. Contingency Table for Drug *i* and Event *j* in Stratum *h*

	Event of interest		
Drug of interest	**Mentioned**	**Not mentioned**	
Mentioned	n_{hij}	$n_{hi.} - n_{hij}$	$n_{hi.}$
Not mentioned	$n_{h.j} - n_{hij}$	$N_h - n_{hi.} - n_{h.j} + n_{hij}$	$N_h - n_{hi.}$
	$n_{h.j}$	$N_h - n_{h.j}$	N_h

N_h is the number of cases in stratum *h*.

Use the above contingency table to define measures of disproportionality

1. Reporting Odds Ratio (Meyboom et al., 1997)
2. Proportional Reporting Ratio (Evans, Waller & Davis, 2001)
3. Multi-item Gamma Poisson Shrinker (DuMouchel, 1999)
4. Bayesian Confidence Propagation Neural Network (Bate et al., 1998; Gould, 2003).

Stratification is an important consideration for disproportionality analysis. How drugs are prescribed, disease severity and how individuals may respond to treatment can all be influenced by demographic and other background characteristics. Therefore, disproportionality statistics should be calculated among homogeneous groups to avoid inappropriate conclusions (Woo et al., 2008).

Pharmacovigilance: Disproportionality Analysis

- How is a signal defined?
  - Each drug-event pair has a confidence or credible interval associated with it
  - If this interval exceeds 1, it is an indication that the event occurs more often for the drug
  - May want a higher threshold
  - May include frequency of events